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Ref. (21)

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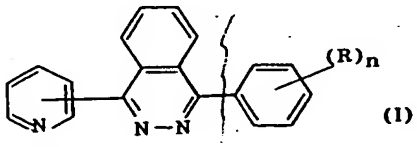
91-175139/24 B02 MORP 20.09.89 *J0 3106-872-A
MORISHITA PHARM KK
20.09.89-JP-246072 (07.05.91) A61k-31/50 C07d-401/04

New 1-substd. phenyl 4-pyridyl-phthalazine(s) - platelet agglutination inhibitors useful as antithrombotics against cerebral thrombosis, cerebral infarction and peripheral arteriosclerosi

C91-075721

B(6-D6, 12-D10, 12-H2, 12-H3) 3 B0172

Phthalazine derivs. of formula (I) are new:



(I)

R = lower alkyl or MeO-;
n = 0-2.

USE

(I) show potent platelet agglutination-inhibiting action and are useful as anti-thrombotic agents in treatment of cerebral thrombosis, cerebral infarction or peripheral arteriostenosis.

Acute toxicity; no lethal cases are observed after oral application at 1000 mg/kg after 7 days in mice.

PREPARATION

Cpd. (II) is reacted with 2-bromobenzoyl chloride under Friedel-Crafts reaction conditions to give (III);

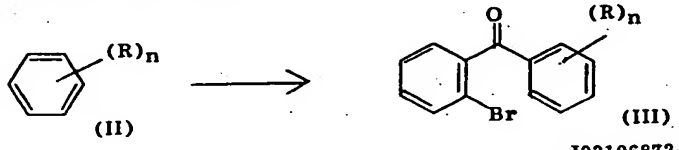
the carbonyl of (III) is protected with 1,3-dioxolane (ethylene ketal);

(IV) is converted into the Grignard reagent, followed by reaction with pyridinealdehyde to give (V);

the hydroxy of (V) is oxidised with e.g. DMSO, Jones agent or Swern agent, to the ketone (VI);

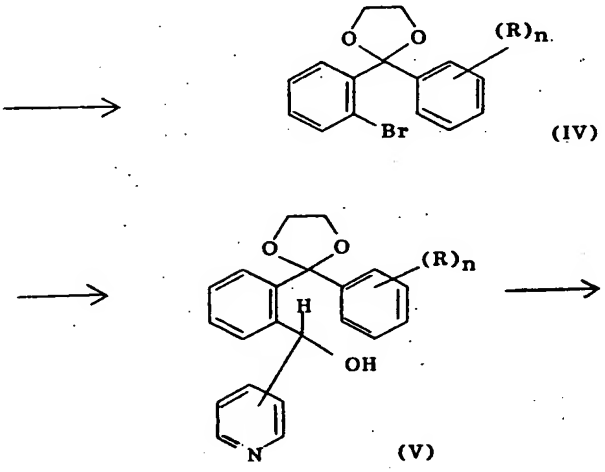
(VI) is deprotected by heating in an acid condition to give the diketones (VII); and

(VII) is reacted with hydrazine in EtOH at room temp. or under refluxing for 0.5-8 hrs.

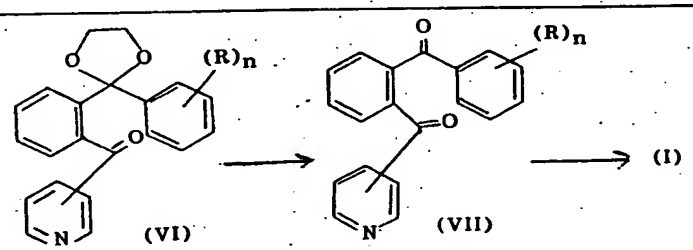


(II) (III)

J03106872-A+



(IV) (V)



(VI) (VII) (I)

EXAMPE

A soln. of 7.0 g. 2-(3-pyridylcarbonyl)phenyl 4-toluyl ketone in 100 ml EtOH was treated with 1.2 g. hydrazine hydrate, and the mixt. refluxed under heating for 2 hrs. After cooling to room temp., the mixt. was evapd. and the residue recrystd. from EtOH to give 2.3 g. 1-(4-toluyl)-4-(3-pyridyl)phthalazine, m.pt. 182-183°C.(7pp W52DAHDwgNo0/0).

J03106872-A

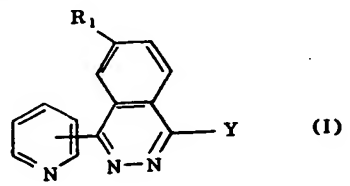
91-175140/24 B02 MORP 20.09.89 *J0 3106-873-A
MORISHITA PHARM KK
20.09.89-JP-246073 (07.05.91) A61k-31/50 C07d-401/04

New 1-substd. 4-pyridyl phthalazine derivs. - are platelet aggregation inhibitors to treat of cerebral thrombosis or infarction or peripheral arteriostenosis

C91-075722

B(6-D6, 12-C10, 12-H2, 12-H3) 3 = ~~22~~ 10a B0173

1-Pyridylphthalazine derivs. of formula (I) and their salts are new:



(I)

R_1 = H or MeO-;
Y = $-NR_2R_3$ (II) or $-X-R_2$ (III);
R_2 = lower or medium chain alkyl, phenyl which may be substd. by halogen or cyano, or opt. substd. pyrimidinyl;
R_3 = H or lower alkyl;
or $-NR_2R_3$ = piperidino, piperazino, morpholino or imidazolyl;
X = O or S-.

USE/ADVANTAGE

(I) show more potent platelet agglutination-inhibiting action than aspirin and are useful as anti-thrombotic agents in treatment of cerebral thrombosis, cerebral infarction or peripheral arteriostenosis.

Acute toxicity: no lethal cases are observed after oral application at 1000 mg/kg after 7 days in mice. (I) may be administered orally or parenterally at a daily dose of 5-2000 (pref. 100-500) mg.

PREPARATION

(I) may be prepd. from 1-pyridyl-4-chlorophthalazine derivs. of formula (IV) on reaction with an amine, alcohol, phenol, mercaptan or thiophene.

J03106873-A+